PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY ~~EXAMINING AUTHORITY~~

To:

Griffith Hack
GPO Box 1285K
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GRIFFITH HACK
1 APR 2004
1 ~~Rec'd~~
2 VS
3

PCT

WRITTEN OPINION
(PCT Rule 66)

Applicant's or agent's file reference fp18189	Date of mailing *(day/month/year)* 31 MAR 2004 **REPLY DUE** within **TWO MONTHS** from the above date of mailing

International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/000972	31 July 2003	1 August 2002

International Patent Classification (IPC) or both national classification and IPC
Int. Cl. [7] C07D 233/90; A61K 31/4172; A61P 1/04, 3/06, 9/10, 9/14, 17/02, 25/28, 29/00, 39/00

Applicant
BIODIEM LIMITED et al

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[X]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

3. The **FINAL DATE** by which the international preliminary examination report must be established according to Rule 69.2 is:
1 December 2004

4. The applicant is hereby **invited to reply** to this opinion.

When? See the **Reply Due** date indicated above. However, the Australian Patent Office will not establish the Report before the earlier of (i) a response being filed, or (ii) one month before the **Final Date** by which the international preliminary examination report must be established. The Report will take into account any response (including amendments) filed before the Report is established.
If no response is filed by 1 month before the Final Date, the international preliminary examination report will be established on the basis of this opinion.
Applicants wishing to have the benefit of a further opinion (if needed) before the report is established should ensure that a response is filed at least **3 months before the Final Date** by which the international preliminary examination report must be established.

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

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WRITTEN OPINION

International application No.
PCT/AU2003/000972

I. Basis of the opinion

1. With regard to the elements of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

V. **Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**1 to 50**	**YES**
	Claims	**nil**	**NO**
Inventive step (IS)	Claims	**2, 14, 16 to 25, 27 to 42, 44, 48**	**YES**
	Claims	**1, 3 to 13, 15, 26, 43, 45 to 47,49, 50**	**NO**
Industrial applicability (IA)	Claims	**1 to 50**	**YES**
	Claims	**nil**	**NO**

2. Citations and explanations

Document 1: Buylon, V.V.. Patologicheskaya Fiziologiya I Eksperimental'naya Terapiya (1995), (1), 21-3. "Central mechanisms of neurogenic gastric lesion and its drug correction".

Document 2: Buloin, V.V, *et al.* Eksperimental'naya Terapiya I Klinicheskaya Farmakologiya(1994), 57(3), 18-20. "Effects of some neurotropic agents on lipid peroxidation in the heart and stomach in their neurogenic damages".

Document 3: Bulyusin, V.Y., *et al.* Byulleten Eksperimental'noi Biologii I Meditsiny (1988), 106(11), 568-70. "Therapy of experimental lesions of the duodenum with nootropic action".

Document 4: Zavodskaya, I.S., *et al.* Biogenic amines (1985), 2(3), 235-41. "Pharmacological analysis of the norepinephrine role in the experimental gastric ulceration".

Document 5: Zavodskaya, I.S., *et al.* Farmakologiya I Toksikologiya (1984), 47(2), 23-8. "Use of neurotropic drugs stimulating tissue trophic processes in the treatment of gastric mucosa ulceration".

Document 6: Zavodskaya, I.S., *et al.* Farmakologiya I Toksikologiya (1983), 46(3), 17-20. "Clinicopharmacological study of some neurotropic drugs in neurogenic diseases of the cardiovascular system and stomach".

Document 7: Chekulaeva, L.I., *et al.* Tkanevaya Biol., Mater. Resp. Soveshch., 2nd (1976), 46-8. "Effect of hydrocortisone and ethymizol on the proliferation of liver and tongue epithelial cells".

Document 8: Anichov, S.V., *et al.* Congr. Hung. Pharmacol. Soc., [Proc.] (1976), Volume Date 1974, 2(6, Symp. Pharmacol. Heart), 59-64.

Document 9: Ketlinskii, S.A., *et al.* Byulleten Eksperimental'noi Biologii I Meditsiny (1977), 83(3), 348-50. "Comparative study of the effect of ethymizol and hydrocortisone on the proliferative activity and protein synthesis in the tongue and liver epithelial cells".

Document 10: Isachenko, V.B., *et al.* Farmakologiya I Toksikologiya (1975), 38(5), 566-8. "Prophylactic and curative action of ethimizol on changes in tissue metabolism of the myocardium during its neurogenic affection".

Document 11: Isachenko, V.B.. Patologicheskaya Fiziologiya I Eksperimental'naya Terapiya (1967), 11(1), 32-5. "Relation between the lipolytic enzyme activity and lipidosis of the aortic wall".

Document 12: Ryzhenkov, V.E..Patologicheskaya Fiziologiya I Eksperimental'naya Terapiya (Moscow) (1967), 30(1), 11-14 "Mode of imidazol- and pyrazoldicarboxylic acid derivatives action on the hypophyseal-adrenal system".

REASONS

Document 1: This document is about the use of ethimizol [in the form of an ionic salt] to retard changes in neurotransmitter balance [those neurotransmitters being norepinephrine, dopamine and GABA]. This mitigated the impairment of energy formation processes in the brain, particularly when the relevant environmental insult was applied to induce damage. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 47, 49 and 50 are not inventive on this further ground.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
RU 2200007	**10 March 2003**	**5 March 1999**	**5 March 1999**

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

Document 2: This document is about the use of ethimizol [in the form of an ionic salt] to retard changes in antioxidative enzyme activity and levels in neurogenic gastric lesions [those antioxidative enzymes being catalase and superoxide dismutase]. This mitigated the impairment of the parasympathetic nervous system and lipid peroxidation processes, particularly when the relevant environmental insult was applied to induce damage. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 47, 49 and 50 are not inventive on this further ground.

Document 3: This document is about the use of ethimizol [in the form of an ionic salt] to mitigate the development of duodenal ulcers. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 47, 49 and 50 are not inventive on this further ground.

Document 4: This document is about the use of ethimizol [in the form of an ionic salt]to enhance the reparative processes with respect to neurogenic lesions of the gastric mucosa. This accelerated the healing of and reduced the number of gastric lesions. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 47, 49 and 50 are not inventive on this further ground.

Document 5: This document is about the use of ethimizol [in the form of an ionic salt] to enhance the reparative processes with respect to gastric mucosa ulceration. This accelerated the healing of these ulcers. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 47, 49 and 50 are not inventive on this further ground.

Document 6: This document is about the use of ethimizol [in the form of an ionic salt] to treat gastric and myocardial damage of neurogenic origin. The salt was also found to be effective in aiding healing from surgery and in patients with ulcers. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 47, 49 and 50 are not inventive on this further ground.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

Document 7: This document is about the use of ethimizol [in the form of an ionic salt] to promote mitotic activity in both tongue and hepatic tissue where the mitotic activity had been suppressed [by hydrocortisone]. In view of this, this document teaches the promotion of tissue repair or wound healing [including in epithelial tissue, being from the tongue], particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of erosions, ulcers, traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 15, 26, 43, 45, 46, 49 and 50 are not inventive on this further ground.

Document 8: This document is about the use of ethimizol [in the form of an ionic salt] to accelerate the repair of damaged heart tissue, especially myocardial tissue. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 49 and 50 are not inventive on this further ground.

Document 9: This document is about the use of ethimizol [in the form of an ionic salt] to promote mitotic activity in both tongue and hepatic tissue where the mitotic activity had been suppressed [by hydrocortisone]. In view of this, this document teaches the promotion of tissue repair or wound healing [including in epithelial tissue, being from the tongue], particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of erosions, ulcers, traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 15, 26, 43, 45, 46, 49 and 50 are not inventive on this further ground.

Document 10: This document is about the use of ethimizol [in the form of an ionic salt] to retard decreases in creatine phosphate and noradrenaline. In view of this it was found to have therapeutic and prophylactic value for damage/injury to myocardial tissue. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt, and especially in the context of traumatic wounds and surgical wounds. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 49 and 50 are not inventive on this further ground.

Document 11: This document is about the use of ethimizol [in the form of an ionic salt] to retard changes due to lipidosis in the aortic wall. In view of this, this document teaches the promotion of tissue repair, particularly with respect to ethimizol in the form of an ionic salt. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 26, 43, 48 to 50 are not inventive on this further ground.

Document 12: This document is about the use of ethimizol [in the form of an ionic salt] to retard inflammations. In view of this, this document teaches the promotion of tissue repair or wound healing, particularly with respect to ethimizol in the form of an ionic salt. Given that *in vivo* this compound would be in an ionic form, the presentation of ethimizol as a salt is uninventive and as a consequence, this renders claims 1, 3, 5, 7, 11 to 13, 15 not inventive. Furthermore this document would directly suggest that simple structural analogues or counter ion variants of ethimizol would possess analogous/comparable properties, and in view of this, claims 1, 3 to 13, 15, 26, 43, 46, 49 and 50 are not inventive on this further ground.